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(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS TO BE TAKEN WITHOUT LIQUIDS, WHICH CONTAIN INCLUSION COMPLEXES

(57) Abstract

Disclosed are pharmaceutical compositions for oral administration which contain inclusion complexes and are characterised by rapid release of the active ingredient and the fact that they require no use of liquids for administration, being the saliva present in the oral cavity adequate for dissolution of the active ingredient. Said formulations are particularly useful in increasing the bioavailability of active ingredients which are insoluble or slightly soluble in water.

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ORAL PHARMACEUTICAL COMPOSITIONS TO BE TAKEN WITHOUT LIQUIDS, WHICH CONTAIN INCLUSION COMPLEXES

Field of the invention

The invention relates to solid oral pharmaceutical compositions capable of rapidly releasing the active ingredient and containing inclusion complexes. The compositions herein described are particularly useful as they require no use of added liquids for administration, being the saliva present in the oral cavity adequate for dissolution of the active ingredient.

State of the art

A problem often faced when administering oral formulations, e.g. tablets or capsules, is that of the difficulty in swallowing which certain patients of categories of patients such as children, the elderly have. Difficult swallowing inevitably causes reduced patient *compliance*. The same happens with persons having irregular access to drink water, such as travelling people or persons with a hectic daily life. In all these cases, drug administration is considerably helped when the intake of solid oral forms does not imply the contemporary intake of liquids or the use of particular devices capable of helping intake.

Some ready-release oral pharmaceutical compositions which permit drug intake with no need to help swallowing of the solid pharmaceutical form with liquids, are already known. In these cases, the formulations disintegrate in the oral cavity. Examples of these formulations are described in patents *Wehling F. et al., US 5,178,878; G. Cousin et al., WO 93/01805; Peters D. et al., US 4,647,450 and Thompson A. R. et al., WO 95/09608.*

One of the problems facing the development of these compositions is the solubility in water of the active ingredients to be released. In fact, all drugs which are defined by the United States Pharmacopoeia *(USP Ed. 23, page 10 (1995))* as slightly soluble (i.e. have a solubility ranging from 1% to 0.1%) or those defined as insoluble (i.e. exhibit a solubility < 0.01%) are usually found to be unsuitable for use in chewable oral formulations. Furthermore, it has also been reported *(Amidon G. L. et al., Pharmaceutical Research 12:413-420, 1997)* that drugs having a low solubility can have significant absorption problems and, hence, bioavailability problems. This makes it difficult to determine the appropriate dose and decide an

appropriate therapeutic line.

One of the means long found to prevent the low bioavailability which is typical of some active ingredients is the use of substances capable of forming inclusion complexes with these active ingredients.

Inclusion complexes are defined as formations made up of a polymeric material and an active ingredient where the active ingredient is included in the polymer. The polymer is used to carry the drug in the aqueous medium and change some of the physical properties typical of the active ingredient. In fact, after the complex has formed, the solubility of the active ingredient in aqueous solvents is usually significantly higher.

Extensive reference to these inclusion complexes can be found in *Kirk Orthmer, Ed. 3, 6:179, 1979*, where the different methods available for their preparation, such as, for example, co-grinding, lyophilisation, spray-drying and granulation, are also described.

For the present invention, in addition to the actual inclusion complexes, the term "inclusion complexes" also includes those pharmaceutical preparations where the active ingredient is supported by a polymeric material which carries it and helps its dissolution.

Additional descriptions of these complexes can be found in the international patent application *Maffione G., WO 94/02177*, where these inclusion techniques are applied in particular to the preparation of complexes with nimesulide. Additional preparation methods are instead described in the United States patents in the name of *Lovrecich M. L., US 5,225,192 and US 5,354,560.*

Usually, in all of the above references the complex is formulated to obtain only traditional oral pharmaceutical forms, thus meant and adapted for conventional absorption in the gastrointestinal tract. These pharmaceutical forms, such as capsules or tablets need to be swallowed, with the above risks of non-compliance by the patient.

These prior art shortcomings highlight the need for more satisfactory oral delivery systems for insoluble active principles. In particular, the need is felt of oral administration systems ensuring high bioavailability of insoluble principles, and involving a simple administration procedure.

Summary of the invention

It is, therefore, a property of the inclusion complexes to increase the apparent solubility of drugs slightly soluble in water, so that the intrinsic dissolution values of the active ingredients included in the inclusion complexes are higher than the corresponding values obtained in the same conditions with non-included active ingredients.

The intrinsic-dissolution values can be determined by the so-called rotating-disk method which, by assuring a consistent surface area for the material subjected to dissolution, precisely allows values typical of the material, free from the influence due to its surface area, to be obtained *(Wood J. H., J. Pharm. Sci., 54:1068, 1965)*.

Theory teaches that, when dissolving a drug in an aqueous medium, a condition of hypersaturation of the medium can be reached when drug concentration is higher than drug solubility in balanced conditions. By acting on the factors which cause hypersaturation conditions, dissolution can be obtained even in environments where such dissolution would not be possible in normal conditions.

The Applicant has now found that the hypersaturation phenomenon can occur even when solid pharmaceutical forms are kept in contact for relatively short times with the limited biological fluids of the mouth rather than be swallowed as is the case with common tablets. In particular, it was surprisingly observed that the hypersaturation phenomenon is helped when, in these pharmaceutical forms, the drug is contained in an inclusion complex. In fact, in such conditions, while the complex polymer swells without dissolving or dissolves slowly, the drug dissolves more rapidly. In this way, even a minor concentration of active ingredient can cause *in situ* the conditions required for hypersaturation. This allows not only rapid development of active-ingredient blood levels, but also, in most cases, improved drug bioavailability related to increased drug absorption.

In addition to improved bioavailability, the easy use of these formulations, which can be taken without adding any liquid in any treatment condition, also implies a significant increase in patient *compliance*.

An object of the present invention is thus a solid oral rapid-release pharmaceutical composition containing inclusion complexes, preferably prepared by co-grinding,

suitable for the administration of the active ingredient in the absence of added liquids.

The inclusion complexes which are part of the invention can include various polymeric materials such as water-soluble complexing agents, hydrophilic linear polymers or swelling reticulated polymers insoluble or slightly soluble in water, and can be prepared by mixing with the active ingredient in varying proportions, depending on the final characteristics desired, using known preparation methods.

Examples of the pharmaceutical forms capable of carrying said inclusion complexes and which are equally part of the present invention include tablets rapidly disintegrating in the oral cavity, chewable tablets, mildly-effervescent tablets to be allowed to dissolve in the mouth, chewable gummy tablets of the chewing-gum type and lyophilised tablets.

Detailed description of the invention

Even though the invention can be adapted to any class of active ingredient, it is particularly suitable for the administration of active ingredients being slightly-soluble or insoluble in water. Among these, the preferred ones are those belonging to drug classes for which rapid development of blood levels is important in order to obtain a ready therapeutic response - such as, for example, analgesics and anti-inflammatory drugs - and those for which it is important to improve poor bioavailability due to absorption problems. Non-limiting examples of these drugs include nimesulide, ibuprofen, indomethacin, flurbiprofen, acetaminophen, acetylsalicylic acid, theophylline, aciclovir, nifedipine, lercanidipine, nitroglycerin, megestrol, sulpiride and the like.

Optionally, depending on the organoleptic characteristics and, in particular, on the taste of the active ingredient, such complexes can also be coated and in some cases microencapsulated.

The materials for active-ingredient inclusion or support complexes which can be used to implement the present invention include:

- water-soluble complexing agents such as, for example, α-, ß-, γ-cyclodextrines and their derivatives such as hydroxypropyl ß-cyclodextrine, sodium carboxymethylamide and the like. Preferred in this class is ß-cyclodextrine.
- hydrophilic linear polymers such as polyvinylpyrrolidone (PVP), cellulose and

their derivatives. Preferred in this class is PVP.

- insoluble or slightly-soluble reticulated polymers which swell upon contact with water such as reticulated polyvinylpyrrolidone (PVP XL), reticulated cyclodextrines, reticulated carboxymethylamide, dextrans. Preferred in this class is PVP XL.

Generally, the active ingredient and the vehicle are in a 1:1 molar ratio in the complex. However, this ratio can be freely changed depending on the peculiar characteristics of the active ingredient and dissolution profile which the drug should advisably possess during administration. Preferably, the active ingredient and the polymeric materials are present in the inclusion complex at a molar ratio ranging from 1:0.1 to 1:10.

The methods of preparation which can be used to prepare the inclusion complexes as defined in this invention can be of a varied nature and are anyhow part of the known art. Among these we can list, for example:

- co-grinding, which is based on intimate mixing by grinding of the active ingredient and inclusion vehicle chosen. A variant of this method which uses high-energy mills to prepare the co-ground material is particularly suitable for the formulations of the present invention as it allows a complex with very small particle size, typically smaller than 10 μm and preferably smaller than 5 μm, to be obtained. Obtaining these particles allows further optimisation of the solubility characteristics of the complex and active ingredient included. Examples of this technique are described in patents *Lovrecich M. L., US 5,225,192 and US 5,354,560.*

- lyophilisation, according to which the active ingredient and polymer are dissolved in a solvent, generally water. The solution is then frozen and the solvent removed by sublimation under vacuum leaving the active ingredient included in the polymer as a residue.

- granulation, according to which the active ingredient is mixed with the polymer in which it is to be included in the presence of organic solvents. After mixing, the solvent is removed by drying.

- spray-drying, according to which the drug and polymer are both distributed in an appropriate solvent. The suspension is sprayed in a hot-air current so that the

solvent can evaporate leaving the inclusion complex as a residue.

Among the above methods, the preferred one is co-grinding due to its extensive applicability. This method, in fact, in addition to avoiding the use of solvents, allows the inclusion complex to be obtained in a finely divided form, thus favourably affecting its solubility.

The pharmaceutical forms capable of carrying the oral compositions to be taken without water and suitable for the present invention include:

- tablets rapidly disintegrating in the oral cavity, where the nucleus contains excipients rapidly disintegrating in water. Examples of these excipients are cellulose derivatives such as carboxymethyl cellulose or low-substituted hydroxypropyl cellulose (L-HPC), polyvinylpyrrolidone XL and carboxymethylamide.

- chewable tablets, made with excipients endowed with good compression and taste characteristics. Typical components include sugars (sucrose, fructose and lactose), polyalcohols (sorbitol, mannitol and xylitol) and microcrystalline cellulose (Avicel^{R}). All of these excipients can be used for preparations by direct compression, with no need to compress the material after prior granulation of the material.

- mildly-effervescent tablets, which contain a mildly-effervescent mixture made up of carbonates and bicarbonates (for example sodium or potassium carbonate or bicarbonate, sodium glycine carbonate) which, in the presence of an organic acid (for example citric acid, tartaric acid) and water, release carbon dioxide.

- chewing-gum tablets, which use diluted gum bases mixed with sugars or polyalcohols (mannitol, sorbitol or xylitol), anti-packing agents (sodium carboxymethyl cellulose) and lubricants (magnesium stearate). The diluted gum bases offer the possibility to make gummy tablets by direct compression.

- lyophilised tablets, which are obtained by lyophilisation of a high-viscosity support made up of sodium or potassium phosphate, citric acid, tartaric acid, gelatine, dextrose, mannitol or dextran. Prior to lyophilisation, the support is filled directly into pre-formed cavities. At the end of the process, the support maintains sufficient consistency, comparable to that obtained by light compression.

To obtain the above pharmaceutical forms, excluding those obtained by

lyophilisation, methods already widely known to those expert in the art, such as direct mixing, dry granulation and compression before final compression, are mostly used. Furthermore, during these steps additional ingredients and additives useful for the presentation of the finished form, including artificial sweeteners, flavours, lubricants or taste enhancers, can be added.

Some examples are being given below which have the only purpose of better describing the subject invention and demonstrating its advantages and applicability, without being a limitation of same.

EXAMPLE 1

No-sugar chewing gum containing nimesulide/ß-cyclodextrine

Chewable gummy tablets (chewing gum) containing nimesulide as the active ingredient in a complex with ß-cyclodextrine equivalent to 100 mg of nimesulide were prepared.

A) Preparation of complex

12 g of nimesulide (0.038 moles) dissolved in 80 ml of a 0.5 aqueous solution of sodium hydroxide was added to 97 g of ß-cyclodextrine (0.076 moles) suspended in 1200 ml of stirred distilled water. The pH of the solution obtained was adjusted to a value of 8.5 and lyophilisation then took place. 98 g of the nimesulide/ß-cyclodextrine complex at a 1:2 molar ratio was obtained.

B) Preparation of tablets

800 g of the nimesulide/ß-cyclodextrine complex prepared in A), 842 g of gum 50% supported on xylitol, 95 g of acacia, 20 g of talc, 7 g of hydrogenated cotton-seed oil Lubritab^{R}, 10 g of lemon flavour, 10 g of orange flavour, 15 g of aspartame, 30 g of liquorice flavour (Glycamil^{R}), 5 g of saccharin and 20 g of silica were transferred into a V mixer. The mixture was mixed for 20 minutes and compressed to a weight of 1854 mg using a convex die with an 18-mm diameter. The tablets so obtained could be sugar-coated with a non-sugary xylitol sugar-coating. Prior to sugar-coating, nuclei were isolated by a varnishing step. An additional amount of lemon extract sufficient to mask the bitter taste of nimesulide was added in the final sugar-coating stage.

EXAMPLE 2

Chewable tablets of nimesulide/ß-cyclodextrine

Rapid-dissolution chewable tablets containing nimesulide as an active ingredient in a complex with ß-cyclodextrine equivalent to 100 mg of nimesulide were prepared.

800 g of the nimesulide/ß-cyclodextrine complex prepared in accordance with paragraph A) in Example 1, 390 g of xylitol, 80 g of polyvinylpyrrolidone XL, 800 g of cellulose ACDISOL, 10 g of magnesium stearate, 20 g of Glycamil^{R}, 10 g of lemon flavour, 10 g of aspartame, were mixed in a V mixer. The mixture was compressed to a weight of 1400 mg per tablet.

EXAMPLE 3

Effervescent tablets of nimesulide/ß-cyclodextrine

Rapid-release mildly-effervescent chewable tablets containing nimesulide as an active ingredient in a complex with ß-cyclodextrine equivalent to 100 mg of nimesulide were prepared.

A) Preparation of complex

2000 g of nimesulide and 7362 g of ß-cyclodextrine were dry-mixed and ground in a high-energy-rotor mill (SWEKO, USA) for 4 hours. In the end, the product was sieved on a 5000-mesh/sq.cm. sieve to ensure product homogeneity and to separate any aggregates.

B) Preparation of tablets

Complex A) so obtained was transferred into a controlled-humidity (< 30%) environment in a TURBULA mixer to prepare 1.0 kg of a mixture having the following composition per tablet: nimesulide/ß-cyclodextrine 400 mg, mannitol 399 mg, aspartame 10 mg, raspberry flavour 60 mg, colloidal silica 1 mg, sodium bicarbonate 100 mg, citric acid 80 mg, magnesium stearate 10 mg. The mixture was then compressed to a weight of 1000 mg/tablet.

EXAMPLE 4

Chewable tablets of ibuprofen/carboxymethylamide

Rapid-release chewable tablets containing ibuprofen as the active ingredient in a complex with carboxymethylamide were prepared. Each tablet contained 200 mg of ibuprofen.

A) Preparation of complex

1000 g of ibuprofen and 2200 g of carboxymethylamide (CMA) were transferred into a high-energy mill (SWEKO, USA). The mill was run up to complete inclusion of ibuprofen into ß-cyclodextrine. Complete inclusion was determined by differential thermal analysis (DSC) observing disappearance of the ibuprofen melting peak. Duration of the process about 3 hours.

B) Preparation of tablets

The following mixture of powdered ingredients was mixed up to a homogeneous mixture suitable for compression having the following composition: ibuprofen/CMA 640 mg, sorbitol 149 mg, cherry flavour 15 mg, aspartame 10 mg, colloidal silica 1 mg, sodium bicarbonate 100 mg, citric acid 80 mg and talc 5 mg, and was added to the complex prepared in A) after sieving. The mixture so obtained was then compressed to a weight of 1000 mg/tablet in an area with controlled humidity lower than 30%.

EXAMPLE 5

Chewable gummy tablets of ibuprofen/carboxymethylamide (CMA)

The ibuprofen/CMA complex prepared as described in part A) of Example 4 was mixed with the following excipients to obtain tablets each containing 200 mg of ibuprofen: ibuprofen/CMA 640.0 mg, gum supported on sorbitol (50/50) 858.7 mg, vanilla flavour 34.0 mg, liquorice flavour (Glycamil^{R}) 80.0 mg, talc 20 mg, hydrogenated cotton-seed oil (Lubritab^{R}) 7 mg, saccharin 0.3 mg. The powder mixture was compressed to a weight of 1640 mg per tablet using a square shaped die.

EXAMPLE 6

Chewable tablets of nifedipine/polyvinylpyrrolidone XL (PVP XL)

Rapid-release chewable tablets containing nifedipine as the active ingredient in a complex with polyvinylpyrrolidone XL equivalent to 5 mg of nifedipine were prepared.

A) Preparation of complex

1000 g of PVP XL were mixed with 2000 ml of a nifedipine solution in methylene chloride (100 mg/ml) in a 10-L Tonazzi apparatus. The mixture was dried under vacuum up to solvent removal.

B) Preparation of tablets

120 g of the nifedipine/polyvinylpyrrolidone-XL complex A), 800 g of lactose, 320 g of polyvinylpyrrolidone XL, 320 g of cellulose ACDISOL^{R}, 120 g of magnesium stearate, 160 g of glycamil^{R}, 240 g of raspberry flavour and 40 g of aspartame were mixed in a V mixer. The mixture was compressed to a weight of 530 mg per tablet.

EXAMPLE 7

***In vivo* release of nimesulide from chewable gummy tablets containing the nimesulide/ß-cyclodextrine inclusion complex**

The amount of nimesulide released in vivo from the formulation prepared according to Example 1 was determined by assaying the nimesulide contained in the residue after chewing for 15 minutes.

Determination was by spectrophotometric reading at a wavelength of 264 nm of the solution obtained after alcoholic extraction of samples chewed for 15 minutes by 5 different individuals. The results obtained from the residue and its complement to 100 (absorbed fraction) are shown in table I below:

TABLE I

Residual nimesulide after chewing for 15 minutes		
Individual	Residual nimesulide (mg)	Fraction absorbed (%)
1	3	97
2	6	97
3	5	95
4	4	96
5	1	99
6	2	98
Mean	3.5	96.5

EXAMPLE 8

***In vitro* dissolution of nimesulide at pH 6.3**

An *in vitro* dissolution test was carried out in conditions simulating the

physiological conditions present in the oral cavity. To this end, the data supplied by the six formulations below were determined:

A = nimesulide (active ingredient)

B = commercial tablets of nimesulide (Aulin^{R})

C = nimesulide/ß-cyclodextrine (complex)

D = nimesulide/ß-cyclodextrine tablets (composition based on the Aulin ® formulation)

E = nimesulide/ß-cyclodextrine tablets (formulation from Example 2)

F = nimesulide/ß-cyclodextrine tablets (formulation from Example 3)

The dissolution properties typical of the active ingredient (A) and those expressed by the commercial nimesulide tablets (Aulin^{R}) having the following composition: nimesulide 100 mg, sodium dioctylsulpho- succinate 1.5 mg, hydroxypropyl cellulose 0.8 mg, lactose 153.7 mg, sodium starch glycolate 35 mg, microgranular cellulose 100 mg, hydrogenated vegetable oil 8 mg, magnesium stearate 1 mg (formulation B), were used as references.

The standards were compared with the properties expressed by the unformulated nimesulide/ß-cyclodextrine complex (C), with the complex formulated similarly to formulation B (formulation D) and with the tablets containing the complex prepared as described in Examples 2 and 3 (formulations E and F).

Each single sample was transferred into a test tube containing 5 ml of phosphate buffer at pH 6.3. After 1, 5 and 10 minutes the solution, filtered from the residue, was read on the spectrophotometer at a wavelength of 264 nm to determine the concentration of nimesulide dissolved.

The values obtained are shown in Table II below as percentages of the amount of nimesulide dissolved from the starting-material complex after 10 minutes.

TABLE II

Dissolution in phosphate buffer pH 6.3						
Times	A (%)	B (%)	C (%)	D (%)	E (%)	F (%)
1	1.4	0.2	98.0	45.8	113.0	112.0
5	2.5	2.5	97.9	64.0	105.0	104.0
10	3.2	3.0	100.0	68.5	103.0	101.0

It is evident from the data shown in the table that:

- nimesulide (A) and the commercial nimesulide tablets (Aulin^{R}) (B) released only minor amounts of active ingredient in the times scheduled.
- the complex with ß-cyclodextrine (C), had a higher release which, for the purpose of the present determination, is considered equal to 100 at the 10-minute time.
- compared to the commercial nimesulide tablets (B), a considerable improvement was obtained when an identical formulation (D) based on the complex with ß-cyclodextrine was used.
- using the formulations (E, F), hypersaturated solutions could be achieved *in situ* in short times and in the presence of little liquid. This provided a rationale for the surprisingly rapid development of the blood levels of active ingredient which can be obtained with these formulations.

CLAIMS

1. A rapid-release pharmaceutical composition for the oral administration, without the help of any added liquids, of an active ingredient slightly soluble or insoluble in water, said composition comprising an active-ingredient inclusion complex with polymeric materials.
2. A composition according to claim 1, characterised by the fact that the active ingredient has a solubility in water ranging from 0.01 to 1%
3. A composition according to claim 2, characterised by the fact that the active ingredient is chosen among nimesulide, ibuprofen, indomethacin, flurbiprofen, acetaminophen, acetylsalicylic acid, theophylline, aciclovir, nifedipine, lercanidipine, nitroglycerin, megestrol and sulpiride.
4. A composition according to claim 1, characterised by the fact that the polymeric materials which form the inclusion complex are chosen among water-soluble complexing agents, hydrophilic linear polymers and water-insoluble swelling reticulated polymers.
5. A composition according to claim 4, characterised by the fact that the water-soluble complexing agents are chosen among α-, ß-, γ-cyclodextrines or their derivatives and sodium carboxymethylamide.
6. A composition according to claim 4, characterised by the fact that the hydrophilic linear polymers are chosen among polyvinylpyrrolidone (PVP), cellulose and their derivatives.
7. A composition according to claim 4, characterised by the fact that the water-insoluble swelling reticulated are chosen among reticulated polyvinylpyrrolidone (PVP XL), reticulated cyclodextrines, reticulated carboxymethylamide and dextrans.
8. A composition according to any preceding claim, characterised by the fact that the active ingredient and the polymeric materials in the inclusion complex are present in a molar ratio ranging from 1:0.1 to 1:10.
9. A composition according to any preceding claim chosen among tablets rapidly disintegrating in the oral cavity, chewable tablets, mildly-effervescent tablets, chewable gummy tablets and lyophilised tablets.
10. A process for the preparation of the inclusion complex described in the

preceding claims, chosen from methods including co-grinding, lyophilisation, granulation and spray-drying.

11. A procedure according to claim 9, characterised by the fact that co-grinding of the ingredients which make up the inclusion complex is carried out in high-energy mills.